Chemotherapy of Leukemia and Leukosarcoma

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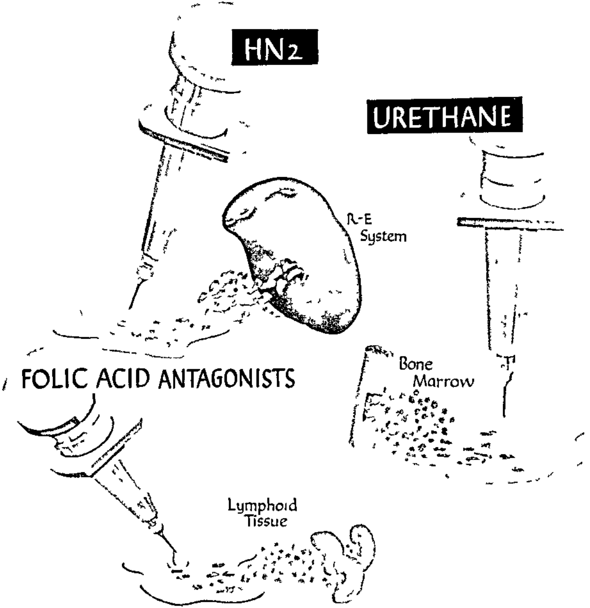
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PREFACE

We know little about the fundamental mechanisms controlling cell growth We know less as to why certain body cells began to proliferate wildly The white cells of the blood forming tissues are also subject to neoplastic proliferation which is likely to be generalized even from the start Surgical extirpation is hardly ever possible, as in local cancer Radium x ray therapy and radio active materials have often proved disappointing The introduction of nitrogen mustard during the war years resulted in a revival of interest in chemotherapeutic methods, coinciding with an awakened interest in the finer histology and histochemistry of individual cells The past few years have witnessed some rather startling developments in the field striking remissions induced by nitrogen mustard in Hodgkin's disease and in some cases of generalized lymphosarcoma, sustained remissions induced by urethane in chronic myelocytic leukemia, modification by urethane of the abnormal marrow and serum protein picture in multiple myeloma and even temporary reversal, thru use of the folic acid antagonists, of the relentless trend towards death in acute leukemia If these accomplishments have occurred within a few years and with our relatively meager knowledge, is it too much to hope that as we know more, there will ultimately come control of our biggest problem in hematology, namely, that of leukemia? This little book, the outgrowth of an American Medical Association exhibit, expresses briefly some of our present-day knowledge in this field, in which much remains to be done

CHEMOTHERAPY OF LEUKEMIA & LEUKOSARCOMA

THE PREMISE *Specific Chemicals kill Specific Cells*

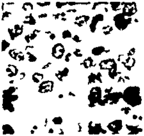
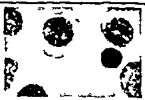


THE HOPE *Ultimate Control of Leukocytic Proliferations Lies in Chemotherapy*

LEUKEMIA AND LEUKOSARCOMA

NEOPLASTIC PROLIFERATIVE DISEASES OF WHITE CELL TISSUES

A CLASSIFICATION

The Leukemias (Leukoses) -- Generalized		The Leukosarcomas (Lymphomas) -- Localized
Myelocytic (Myelogenous) Acute - Subacute Chronic (Eosinophilic-Basophilic types very rare)		Myelosarcoma (Chloroma) Very rare
Lymphocytic (Lymphatic) Acute Subacute Chronic		Lymphosarcoma Lymphoblast Sarcoma Lymphocyte Sarcoma Leukemia Cutis Giant Follicle Lymphosaroma
Monocytic Acute Subacute Chronic		Reticulosarcoma Reticulum Cell Sarcoma Hodgkin's Disease (rapid, "Sarcoma") Reticulo-endothelioma Hodgkin's Disease (slow, "Granuloma") Mycosis Fungoides
Plasmacytic (Multiple Myeloma)		Plasmacytoma (Solitary Myeloma)

The Leukemias (Leukoses) are either Leukemic or Aleukemic
The Leukosarcomas, generally Aleukemic, may become Leukemic

LEUKEMIA AND LEUKOSARCOMA

A SCHEMA

Correlating Cell Growth Rate with Clinical Activity

LEUKEMIAS GENERALIZED	LEUKOSARCOMAS LOCALIZED

CELL GROWTH RATE EXTREMELY RAPID

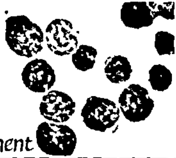
"Acute"
- All cells primitive
- No differentiation
- Fulminating course (1-8 wks)
- Rapid Marrow Involvement
  - Anemia, Granulocytopenia
  - Thrombocytopenia
  - Bleeding



"Blast" Sarcoma
- Nucleoli very prominent
- Many Mitoses
- Highly Invasive
- Widely Metastatic
  - Bone, Lungs, etc.

CELL GROWTH RAPID

"Subacute"
- Most Cells primitive
- Some differentiation
- Less Rapid Course
  - (8 wks. – 1 yr.)
- Marked Marrow Involvement



"Blast-Cyte" Sarcoma
- Nucleoli fewer
- Fewer Mitoses
- Invasive
- Metastatic

CELL GROWTH RATE RELATIVELY SLOW

"Chronic"
- Most cells mature
- Marked differentiation
- Slow course (1-10 yrs.)
- Slow marrow involvement

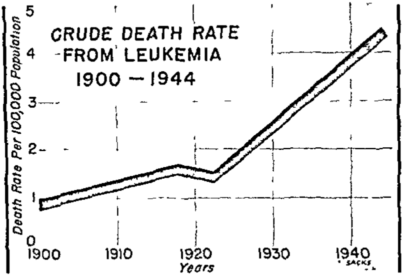


"Cyte" Sarcoma
- Few nucleoli
- Few Mitoses
- Relatively benign
- Slowly invasive

LEUKEMIA AND LEUKOSARCOMA

ETIOLOGIC FACTORS

Death rate for Leukemia shows sharp Increase.
Is this better diagnosis? Actual increase? Both?
If actual increase, why? Maybe it's Civilization.



POSSIBLE HAZARDS TO BLOOD FORMING TISSUES IN "CIVILIZED" LIVING
SOME SPECULATIONS

CHEMICAL EXPOSURE

Medications: Sulfa Drugs, other Benzene Drugs
Skin Lotions & Ointments
Phenol Tars
Unsupervised use of Potent Growth Factors (vitamins, hormones)
Industry: Benzol Xylol, Solvents
Farming: Insecticides, (Arsenic)
Roads: Tars, Gases
The Home: Lotions, Cosmetics, Paint removers.
Foods. Chemical Preservatives

RADIATION EXPOSURE

Occupational: Radiologists
X-ray technicians
Atomic energy personnel
Cyclotron workers
Too many X-ray examinations
X-ray Therapy: Thymus in infancy
: Skin Disease
Radio-Active Isotopes
Atomic bombs

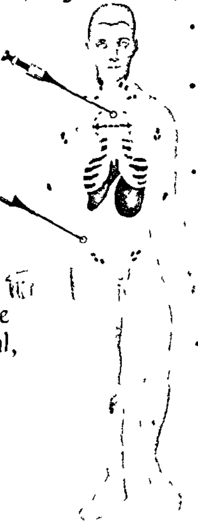
OTHER FACTORS: HEREDITY, INFECTION (VIRUSES?) MAY BE IMPORTANT

LEUKEMIA AND LEUKOSARCOMA
DIAGNOSTIC TRIAD

I. History: Fatigue, Fever, Night Sweats, Itching, Bleeding

II. Examination

- Head:
  - Pallor, icterus
  - Conjunctivae, Retinae
- Mouth: Tongue
  - Gums: Hyperplasia
  - : Bleeding
  - Buccal mucosae
- Throat: Tonsillar ++
- Glands:
  - Mickulicz' Syndrome
    - Parotid, Lachrymal,
    - Submaxillary
- Abdomen:
  - Hepatomegaly
  - Splenomegaly
  - Masses



- Neck: Lymph Nodes
  - Other masses
- Chest:
  - Supra-Cardiac Dullness
  - Sternal - tenderness
- Lymphadenopathy
  - Cervical
  - Supraclavicular
  - Axillary
  - Epitrochlear
  - Inguinal
- Extremities:
  - Petechiae, Ecchymoses
  - Bone Tenderness
- Skin: Rash
  - Hemorrhages
  - Edema

III. Laboratory Data

- Blood Counts. Smears All-Important
  - Recognize Primitive Cells
  - And Diminished Platelets
  - Sedimentation Rate. Serum Proteins
- Xrays: Mediastinum
  - Bones
  - Spleen Size



- Bone Marrow
  - Puncture: Sternum, Iliac Crest
    - Spinous Process
  - Trephine Biopsy: occasionally
- Tissue Biopsy: Lymph Nodes
  - Biopsy, Aspiration, Imprints
  - Skin
  - Liver, Spleen

LEUKEMIA & LEUKOSARCOMA
CYTOLOGIC STUDIES

Minute Study of the Cell has become All-Important
- To reveal secrets of Cell Growth and Death
- To aid in selecting specific drugs

A diagnosis of "Acute Leukemia" is not enough
- Is it Myeloblastic, Lymphoblastic, Monocytic?

METHODS NOW IN GENERAL USE

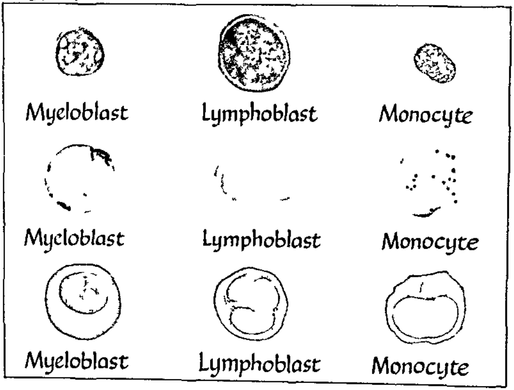
I. Correlation with Clinical Features

Splenomegaly :	Myeloblastic
Lymphadenopathy :	Lymphoblastic
Gingival Hyperplasia :	Monocytic

II Romanowsky Stains (e.g. Wrights)

III Peroxidase Stains (e.g Sato-Sekiya

IV Supravital Stains (e.g. Janus Green, Pinacyanol)

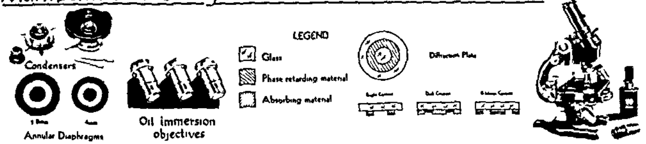


- Sometimes, these methods fail to make a definitive diagnosis
  - Newer Cytologic techniques reveal Fundamental Structures.

NEWER AIDS IN CYTOLOGIC STUDIES

PHASE MICROSCOPY

Manipulation of light waves achieves contrast



These + These + Diffraction Plates = Phase Microscopy

- Can Adjust contrast by different diffraction plates
  1. Bright Contrast --- object brighter than background
  2. Dark Contrast --- object darker than background
- Great Clarity and Contrast achieved in the study of:
  - Unstained living cells
  - Unstained fixed cells
  - Supravital preparations
  - Histochemical reactions (counterstains not necessary)



Unstained Cell in Smear
Ordinary Microscope



Unstained Cell in Smear
Phase Microscope



Myeloblast Lymphoblast Monocyte — Sudan Black

Myeloblast Lymphoblast — Supravital-Pinacyanol

(Phase Photomicrographs)

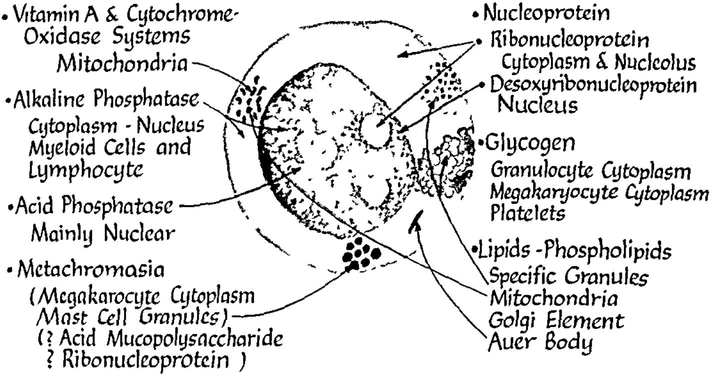
- Phase Microscopy often discloses materials previously invisible

NEWER AIDS IN CYTOLOGIC STUDIES

HISTOCHEMISTRY - Study of the Chemistry of Individual Cells

- Histochemical studies may open up new vistas for attacking Proliferating Cells

THE WHITE CELL AND SOME OF ITS CONSTITUENTS (1949)



SUDAN BLACK B

- An Important Histochemical Tool. Defines Lipids.

In dry smears defines patterns previously seen only in Supravital Preparations
Reacts with Specific Granules, Auer Bodies, Mitochondria, Golgi Element



Leukemic Myeloblast



Leukemic Lymphoblast



Leukemic Monocyte

THE THERAPY OF LEUKEMIA & LEUKOSARCOMA

HISTORICAL

ARSENIC
First Chemotherapeutic Agent used (1865)

BENZOL
Used in early 1900's; found too toxic

X-RAYS
Became prominent after 1910; in wide use since

RADIO-ACTIVE ISOTOPES
Continued experience indicates very limited value

XRAYS AND CHEMOTHERAPY: A COMPARISON

X-rays
Diffuse
Non-Selective



Chemicals
May have specific actions on specific cell mechanisms

NITROGEN MUSTARDS
Shown to have tissue effects like X-rays (1942)
Special value in Hodgkin's Disease and Lymphosarcoma

URETHANE (1946) AND FOLIC ACID ANTAGONISTS (1948)
Show distinct promise in Leukemia

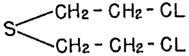
Although X-ray still the Standard ℞
Chemotherapy offers more for the future

THE "MUSTARDS"

POISON GASES TO USEFUL DRUGS

SULFUR MUSTARD

SULFUR MUSTARD



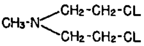
Bis (B Chloroethyl) Sulfide

Sulfur Mustard Gas killed many in World War I.

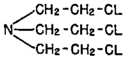
The more deadly Nitrogen Mustards ready in World War II

NITROGEN MUSTARDS

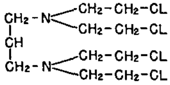
NITROGEN MUSTARDS



Methyl Bis (B Chloroethyl) Amine (HN2)



Tris (B Chloroethyl) Amine (HN3)



1,3 Propane Diamine N N N' N' Tetrakis 2 Chloroethyl (SK 136)

- Pharmacologic studies revealed marked Leukopenic effect
- Possible value in W.B.C. proliferations was suggested
- Thus, a Poison "Gas," properly controlled, became a Useful Drug

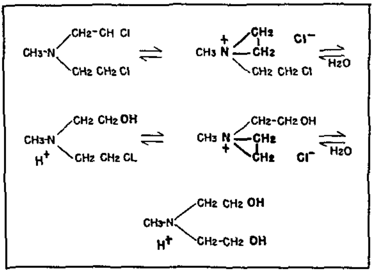
NITROGEN MUSTARDS

PHARMACOLOGY

- Nitrogen Mustards are readily soluble. Dissolved in water, rapid transformations occur, producing cytotoxic effects within few minutes

TRANSFORMATIONS

"Intramolecular Cyclization" (Gilman and Philips)



Highly reactive Onium Cation and Liberation of Cl

<u>Numerous Cellular Enzyme Systems inactivated:</u>

Hexokinase, Pyrophosphatase, Diaminase, Cholinesterase, Choline Oxidase, Pyruvate, Phosphokinase, Phosphatase, Peptidase, Pyridoxine, etc.

LEADING TO DEATH OF PROLIFERATING CELLS

<u>Nuclear, Mitotic, Chromosomal activities sharply affected</u>

Involution of normal Lymphoid tissue
Desquamation of Intestinal Epithelium
Hypoplasia of Marrow
Regression of Lymphosarcoma and Leukemia in experimental animals

<u>The Mustards, altho chemicals, act much like X-rays</u>

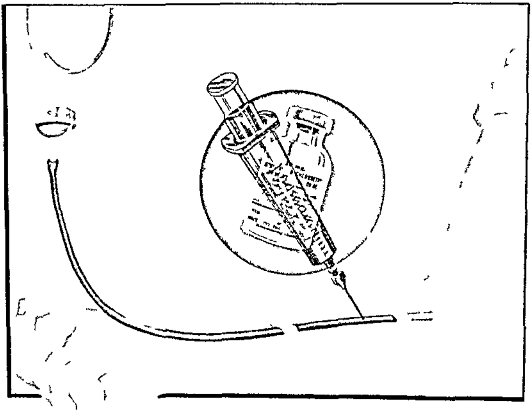
NITROGEN MUSTARDS

ADMINISTRATION

Dosage:

About 0.07 - 0.08 mg./kg. body weight
Course: 4-6 injections-given once daily
First Dose - 3-5 mgs.: Increase by 1 mg. daily
Course may be repeated in 8 - 10 weeks

Mode of Administration:



Immediate Reactions: Nausea and Vomiting in 1-2 hours
lasting 1-3 hours
Occasional chills and fever

NITROGEN MUSTARDS

THERAPEUTIC ACTIVITY

Clinical trials with HN_2 and HN_3 in:

- Acute Leukemia: No definite effects
- Chronic Leukemia: Equivocal effects
- Lymphosarcoma: Good effects in some
- Hodgkin's Disease: Good effects frequently

In Hodgkin's Disease:

Most striking effects seen in advanced, generalized, X-ray refractory cases

RESULTS IN 50 CONSECUTIVE SEVERE CASES

SYMPTOMATIC RESPONSE

	% COMPLETE RELIEF	% PARTIAL RELIEF	% NO RELIEF
* Fatigue	45	42	13
* Anorexia	67	22	11
* Sweats	83		17
* Itching	44	44	12
Pain	79	11	10
Cough	30	30	40
Dyspnea	20	53	27
Hoarseness		13	87
* Chills	83		17

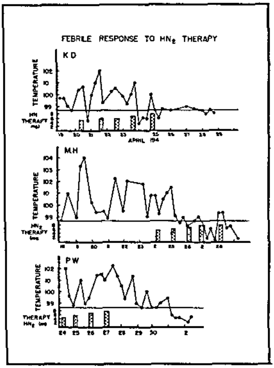
OBJECTIVE RESPONSE

	% COMPLETE RELIEF	% PARTIAL RELIEF	% NO RELIEF
Fever	47	15	38
Weight Loss	65	32	3
Lymphadenopathy	48	33	19
Mediastinum	29	39	32
Splenomegaly	38	35	27
Hepatomegaly	32	16	52
Edema	13	46	41
Paralysis		44	56

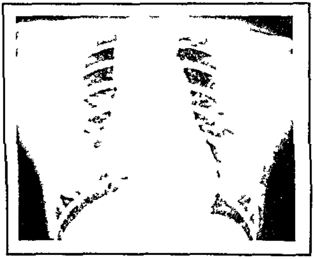
* Constitutional symptoms and pain most strikingly affected

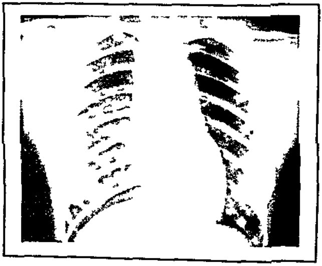
About 80% of the cases showed Responses

HN2 THERAPY IN HODGKIN'S DISEASE
EFFECTS ON FEVER AND LYMPHADENOPATHY



Fever usually subsides 1-4 days after HN2 completed.
Fever response may be used as a diagnostic measure

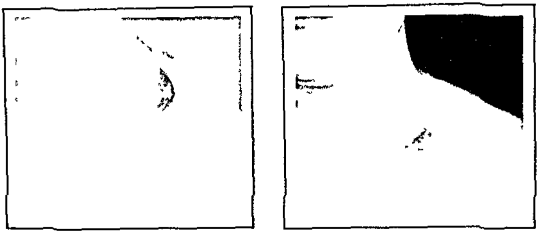




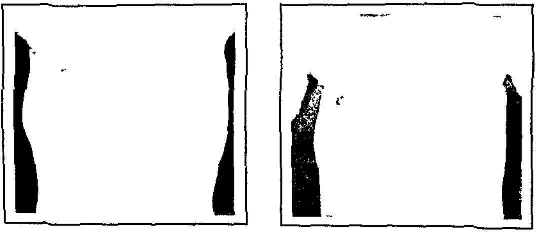
BEFORE Rx *3 WEEKS AFTER Rx*

- Mediastinal Lymphadenopathy subsides most quickly in least fibrotic cases

HN_2 THERAPY OF HODGKIN'S DISEASE



X-ray Refractory Left Supraclavicular Mass
Before and After one course of HN_2 ℞

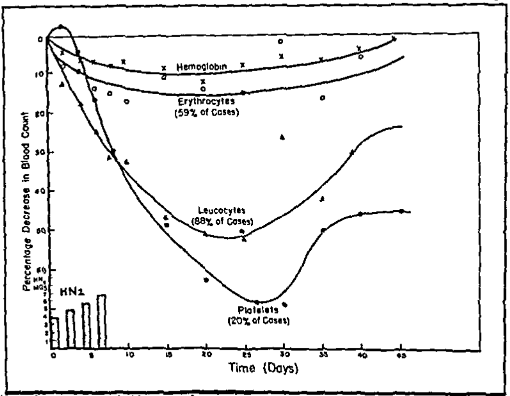


Terminal X-ray Refractory Case with Right Thoracic Mass
Before and After one course of HN_2 ℞

<u>HN_2 is often successful in X-ray Refractory Cases.</u>

HN_2 THERAPY IN HODGKIN'S DISEASE

<u>Tissue Reactions</u>: Bone Marrow Hypoplasia* develops quickly
Blood shows reduction in white cells, mostly Granulocytes

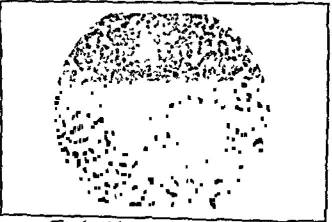


Lymphoid Tissue Affected:



Miliary Necrosis in Lymphnode

Liver Occasionally Involved:



Toxic Necrosis in Liver

- Beware excessive dosage of HN_2
- Jaundice contraindicates use of HN_2

*See Translites

HODGKIN'S DISEASE

A NEOPLASM OF RETICULUM CELL ORIGIN

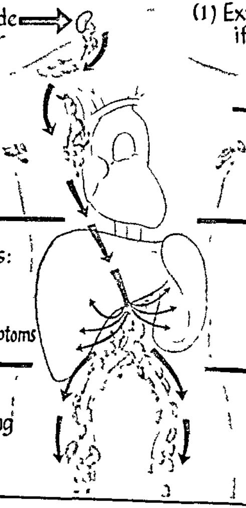
Growth rate and course highly variable

Most malignant: Many Giant Cells, little Fibrosis ("Sarcoma" type)
Most benign: Few Giant Cells, much Fibrosis
Most cases: Giant Cells, Fibrosis, Eosinophilia

These are not separate diseases, but represent variations in growth rate

We do not consider Hodgkin's an Infection or a "Granuloma"

COURSE



STAGE 1

SYMPTOMS

Begins in one Lymph Node a painless, non-tender lump

TREATMENT

(1) Extirpate Lymph Node Mass if possible.
(2) X-ray Rx
(3) HN2 Rx

STAGE 2

Spreads to group of Nodes
Fatigue, Fever

(1) Drastic X-ray Rx
(2) HN2 Rx

STAGE 3

Involves Central Organs: Spleen, Liver, Bones Mesentery, Spinal Cord

Many Constitutional Symptoms

(1) HN2 Rx best
(2) X-ray Rx as adjuvant

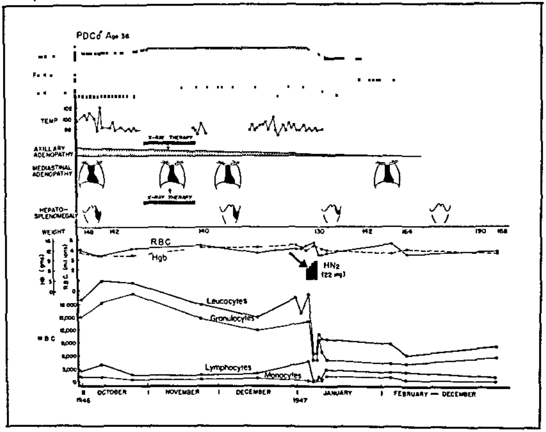
STAGE 4

Becomes Universal
Extreme Debility, Relapsing Fever, Bone Pains, Cachexia, Death

(1) Try HN2 Rx
(2) Symptomatic Rx
Transfusions

HN2 THERAPY IN HODGKIN'S DISEASE

Case Report: P.D.C. Generalized Hodgkin's (STAGE III)



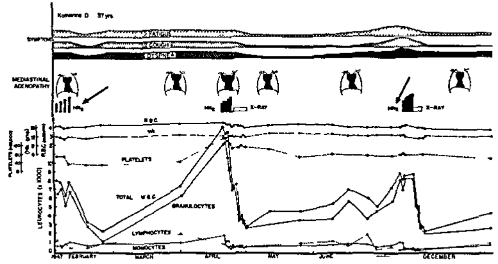
Persistent fatigue, fever, weight loss, splenomegaly, despite X-ray treatment.

NOTE: Striking effect of HN2 on constitutional symptoms.
Gain in appetite, vitality, and weight (60 LBS.)
Striking effect on Lymphadenopathy, Splenomegaly.
Remission persisted 18 months

HN2 most useful in generalized and refractory cases.

HN2 THERAPY IN HODGKIN'S DISEASE

<u>Case Report</u>: Katherine D. Severe mediastinal disease 5 years. Progressive X-ray refractoriness.



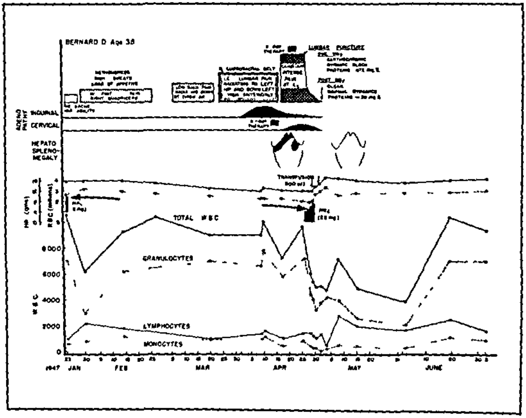
<u>*NOTE:*</u> Enhancement of X-ray effect by previous HN_2 Rx
: Improvement lasting 4 months with combined Rx

HN_2 enhances X-ray sensitivity; HN_2 plus X-ray prolongs remission.

HN_2 (generalized effect) plus X-ray (local effect) may be valuable in early cases

HN₂ THERAPY IN HODGKIN'S DISEASE

Case Report: B.D. Hodgkin's since 1944 - X-ray refractory 1946
HN₂ induced 6 month remission;
Development of back pain, January 1947

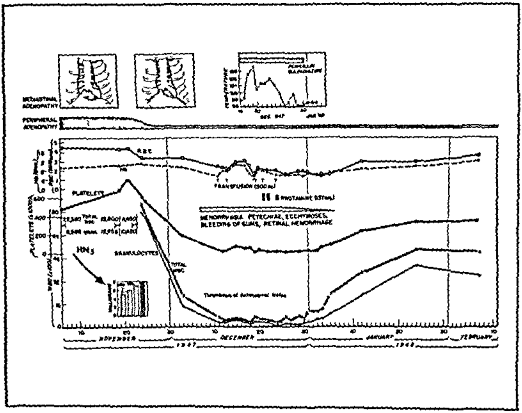


NOTE. Lack of response of back pain to X-ray treatment
: Complete dynamic block of spinal fluid & extremely high proteins
: Response to HN₂ almost incredible: Pain relief in 24 hrs.
Continues (JUNE 1949) free of pain & still responsive to HN₂ treatment

Pain due to intra-or extraspinal lesions of Hodgkin's often quickly and completely arrested.
Paralysis of intraspinal involvement responds poorly unless treated early

TRIS MUSTARD (HN_3) THERAPY IN HODGKIN'S DISEASE

Case Report: Mary S. Hodgkin's "Sarcoma"
℞ with HN_3. Aplastic Anemia

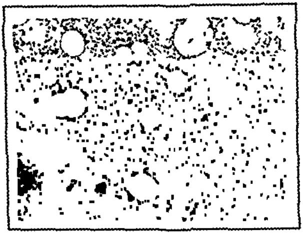


NOTE: Marrow Aplasia:* Pancytopenia
: Active Symptomatic Therapy: Recovery
: Patient continues well: Relapses respond to HN_2 and X-ray

Tris Mustard more toxic than Bis form
Hodgkin's "Sarcoma" often very sensitive to Mustard ℞
Marrow reactions usually improve spontaneously

*See Translites

THE EFFECT OF TRIS MUSTARD (HN_3) THERAPY ON BONE MARROW



Before ℞



Eight days after ℞
Hypocellularity



20 days after ℞:
Marked Hypocellularity



38 days after ℞
Beginning Marrow Recovery

Although Nitrogen Mustards cause Marrow Hypoplasia, no permanent Aplasia has followed our low dosage.

HN_2 Rx IN LYMPHOSARCOMA

HN_2 Rx in Lymphosarcoma may produce remarkable Remissions
21 consecutive cases of Generalized Lymphosarcoma
7 showed complete Remissions of 6 to 24 months

Case Report: "Terminal" Generalized Lymphosarcoma, X-ray Refractory
Remarkable response with one course of HN_2

Ferne B. Age: 49 April, 1947

History:
1945: Lumps in Axillae
: Biopsy: Giant Follicle Lymphoma
: X-ray Rxs almost constantly
Feb.'47: X-ray Rxs of spleen, neck, axillae, left eye (exophthalmos)
Apr '47: Extreme Dyspnea
Extreme weakness
50 lb. weight loss

P.E.
Weight 122 lbs.
Extreme Dyspnea, Cachexia
Masses of Lymph Nodes: Neck, supraclavicular, axillae, groins.
Splenomegaly 3-4 f.b.
Fluid Both Chests
Swollen Legs

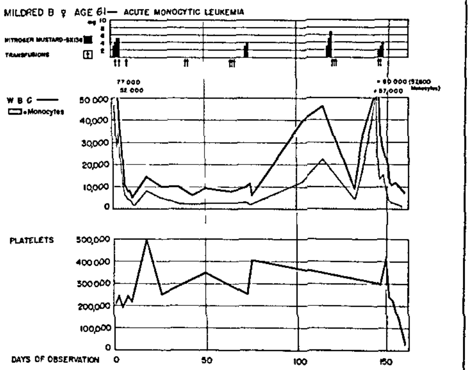
Lab. Data:
Hgb. 11.7 gms.
R.B.C. 3.95 M.
Retics. 0.8 %
Platelets 337,000
W.B.C. 2800; P.59, L.17, M.22
Lymph Node Biopsy: Lymphoblast Sarcoma, highly malignant.
X-ray chest:
Fluid bilaterally;
Mediastinum +++

Course
HN_2 Rx, 22 mgs. (4 injs.) Apr. 13-17, '47
Apr. 25: No Lymphadenopathy
Spleen 1 f.b.
Sept. 16: No symptoms; weight 128 lbs
Spleen not felt
P.E. negative
Nov. 17: Weight 134 lbs.
Jan. 14: Goes to gym; plays badminton
Apr. 6: Weight 143 lbs.
Looks 20 yrs. younger
Jan.'49: Continued excellent health

"SK-136": ANOTHER MUSTARD

<u>SK 136 is one of a large group of Mustards tried clinically</u>

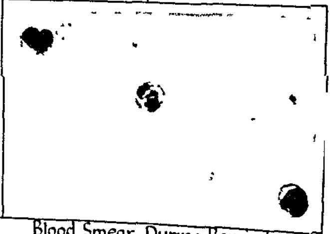
No particular value in Hodgkin's disease
Slight value in Chronic Myelocytic Leukemia
Some value in Acute Monocytic Leukemia



Acute Monocytic Leukemia

Definite Remissions Induced





Blood Smear Before SK 136 — Blood Smear During Remission

Other types of Acute Leukemia (10 cases) not affected by SK-136
Other Mustards may prove of specific value for specific cells

THE NITROGEN MUSTARDS

CONCLUSIONS

In Hodgkin's Disease HN_2 is indispensable:

In generalized, X-ray Refractory cases
To relieve pain and constitutional symptoms
In conjunction with X-ray, may prove valuable in early cases
Many "Terminal" cases salvaged for 6-36 months.

In Lymphosarcoma and Reticulum Cell Sarcoma

HN_2 worth a trial, especially in generalized cases
A few injections may cause a startling Remission

In Acute Leukemia

"SK-136" may be of temporary benefit in monocytic type

- Used with Care and Discretion
  the Mustards are Useful Drugs

THE NITROGEN MUSTARDS

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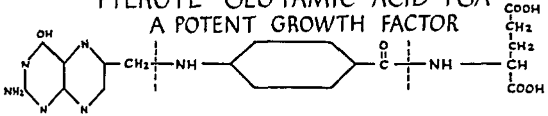
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- Used with Care and Discretion
  the Mustards are Useful Drugs

FOLIC ACID

PTEROYL GLUTAMIC ACID PGA

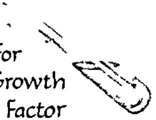
A POTENT GROWTH FACTOR

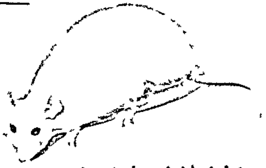


PTERIDINE RING *P-AMINOBENZOIC ACID* *GLUTAMIC ACID*

Originally found in Liver Extract Residues: A fraction of B complex
Folic Acid Synthesized 1945
Conjugates (E.G. TRIGLUTAMIDE) formed by adding extra Glutamic Acids

---





• Necessary for Bacterial Growth (L. Casei Factor Strep. Fecalis R Factor)

• Important in Animal Nutrition

PGA or CONJUGATES

• Important in White Cell Growth



Deficiency → Leukopenia

• Enhance Growth of Certain Neoplasms

• Inhibit Growth of Certain Neoplasms (Triglutamide -Teropterin)



• High Content in Primitive White Cells (Bethell)



• Red Cell Growth Factor Deficiency - Megaloblastic Marrow (cf. P.A., Sprue, etc.)

Knowledge of these effects led to Synthesis of PGA Antagonists

FOLIC ACID ANTAGONISTS

POTENT GROWTH INHIBITORS

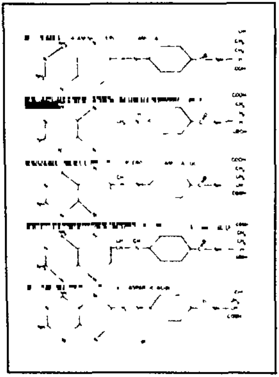
Certain alterations of PGA Molecule create powerful Antagonists to PGA



PGA (Folic Acid) — GROWTH FACTOR

PGA Antagonist (Aminopterin) — GROWTH INHIBITOR

NUMEROUS ANTAGONISTS HAVE BEEN SYNTHESIZED



- Inhibit growth of bacteria
- Prevent normal growth in animals
  Chick Pig Rat
  Dog Mouse
- Inhibit normal Marrow growth:
  Leukopenia, Anemia, Thrombopenia
- Inhibit growth of Rous Chick Sarcoma
- Act on other Tumors
  Carcinolytic activity
- Act on Animal Leukemia
  and Leukosarcoma

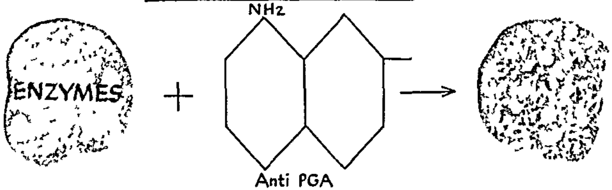
FOLIC ACID ANTAGONISTS

Exact Mode of Action Uncertain

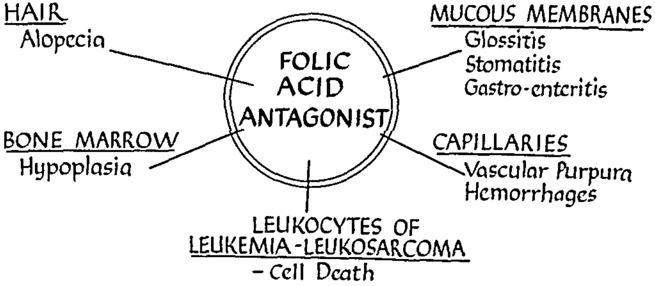
ONE POSSIBILITY

Anti-PGA resembles PGA so closely that it is readily accepted by cell, but cannot be utilized

Result: Cell Death



In the human body the Folic Acid Antagonists affect numerous tissues

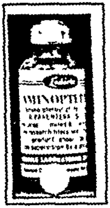


Clinical Trials indicated its use in Acute Leukemia

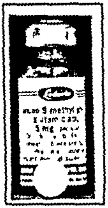
FOLIC ACID ANTAGONISTS

PATTERN OF THERAPY IN ACUTE LEUKEMIA

I. Give Drug



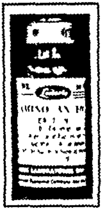
AMINOPTERIN
1-4 MGS



A-NINOPTERIN
5-15 MGS



A METHOPTERIN
2-5 MGS



AMINO-AN-FOL
25-75 MGS

Dose varies with Drug, Age, W.B.C.
Oral Medication as effective as Parenteral

II. Watch for reactions and marked drop in W.B.C.
Anorexia, Sore Mouth, Nausea, Diarrhea, Abdominal Discomfort, Mucous Membrane Lesions, Hemorrhagic Rash

III. Stop Drug at first sign of reaction

IV [illegible]
[illegible] as indicated

V. Watch for Remission
Rise in Platelets particularly, fall in W.B.C. and 'blasts

VI. Give Maintenance Therapy, usually oral
Aminopterin 1/4 to 1 mg. daily; A-ninopterin 5 mgs. daily

Adjust dosage according to further reactions or relapses

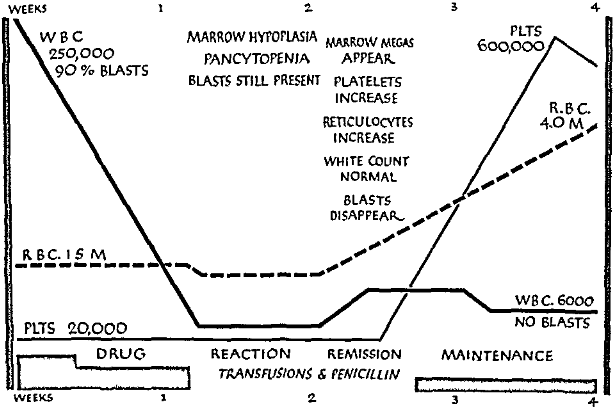
FOLIC ACID ANTAGONISTS

CLINICAL EFFECTS IN ACUTE LEUKEMIA

I. Reaction

II. Remission (Occurs in one-third of the cases)

Subjective	Objective
Appetite ↑	Fever ↓ Weight ↑
Activity ↑	Lymph Nodes ↓ Splenomegaly ↓
Well Being ↑	General Appearance ↑
Irritability ↓	Hemorrhagic Phenomena ↓



Remission continues with maintenance therapy 1 to 12 mos.

III. Relapses occur. More Drug: More Remission

IV. Finally: Relapses + Increasing Toxicity → Death

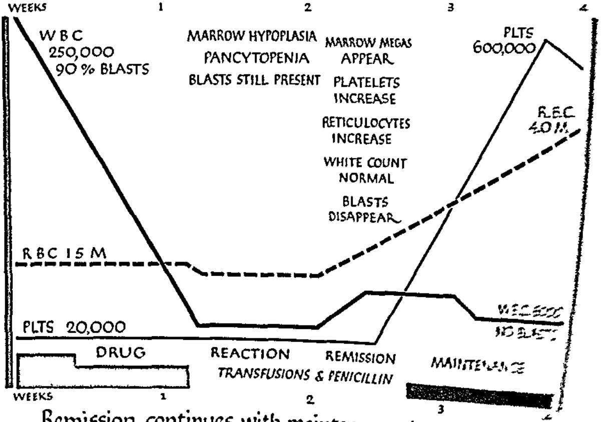
FOLIC ACID ANTAGONISTS

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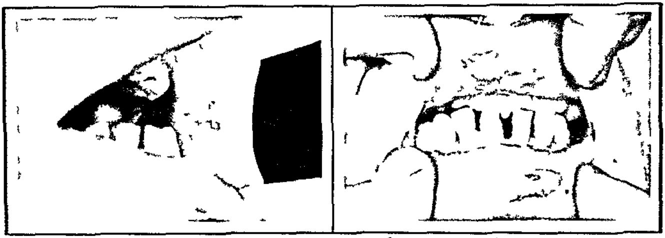
Remission continues with maintenance therapy [illegible]

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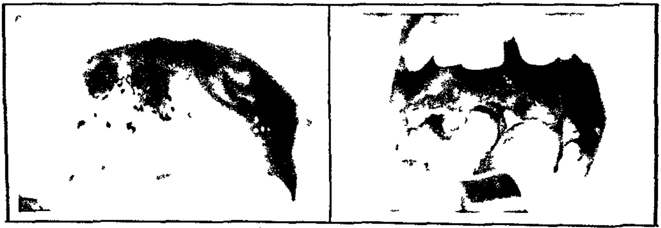
IV. Finally: Relapses + Increasing Toxicity → Death

FOLIC ACID ANTAGONISTS
℞ OF ACUTE LEUKEMIA

REACTIONS



Redness and Ulceration of Buccal Mucosae



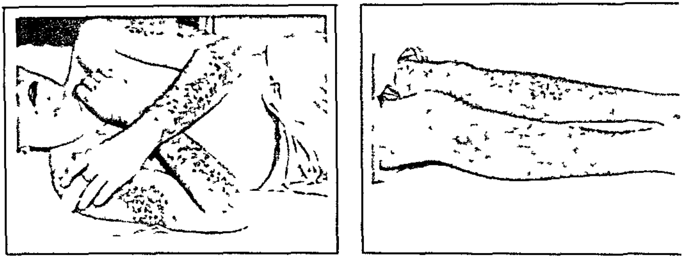
Palatal Lesions

- Lesions also occur in lower gastro-intestinal tract

FOLIC ACID ANTAGONISTS

Rx OF ACUTE LEUKEMIA

REACTIONS



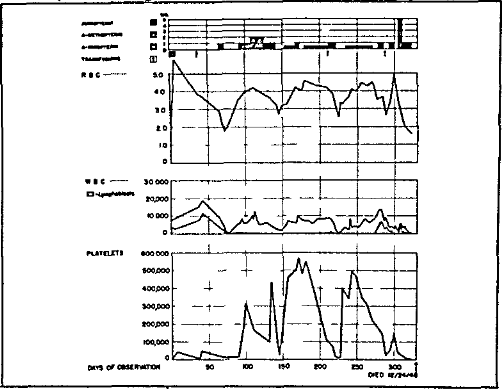
Vascular Purpura: Aggravated by Thrombocytopenia



Alopecia develops slowly
Brown Pigmentation of Skin also occurs

FOLIC ACID ANTAGONISTS: ℞ OF ACUTE LEUKEMIA

Case Report: Joseph C. 3½ yrs. Subacute (Aleukemic) Lymphocytic Leukemia





At end of first Remission

Note:

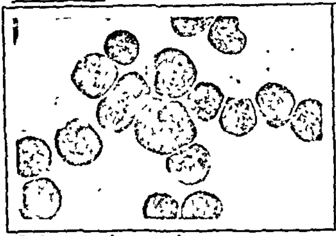
2 separate Remissions induced
Remission heralded by: Platelet increase
: Megas. in marrow
Patient lived 8½ months

Death due to: Increasing Leukemia
: Increasing Toxicity

FOLIC ACID ANTAGONISTS:
℞ OF ACUTE LEUKEMIA

· RESPONSE ON PART OF MARROW ·

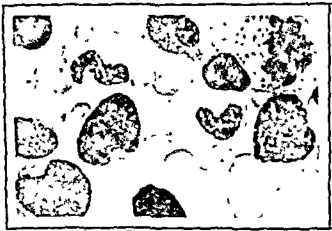
Case J.C. (CONTINUED)



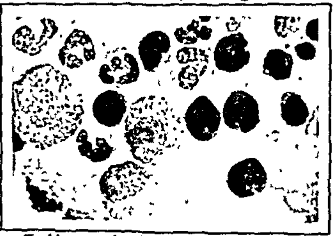
Before Aminopterin:
All Lymphoblasts



Beginning Remission:
Megakaryocytes



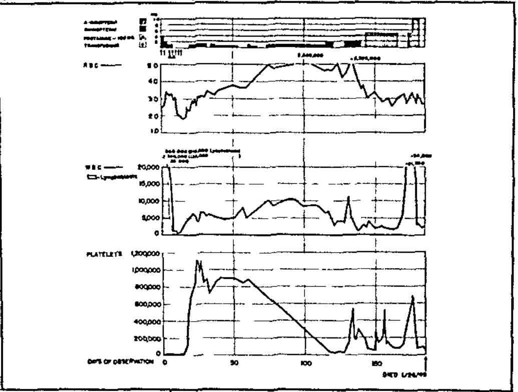
Beginning Remission:
Normal Marrow
Cells;
Lymphoblasts



Full remission but few
Lymphoblasts persist

FOLIC ACID ANTAGONISTS: ℞ OF ACUTE LEUKEMIA

Case Report: Katherine B. Age 29. Subacute Lymphocytic Leukemia





At end of first remission

Note:

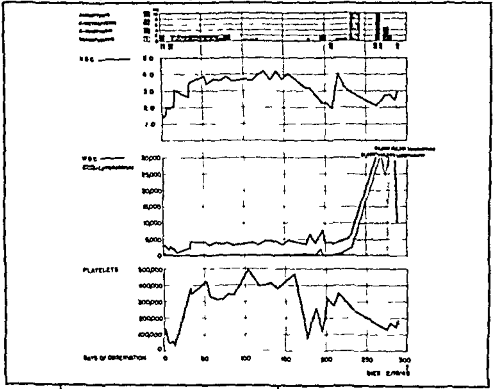
- Severe reaction before remission
- Platelet increase beginning remission
- Complete Marrow & Blood remission
- Development of Torula Meningitis

Death in 6 months

Death due to Meningitis + Leukemia

FOLIC ACID ANTAGONISTS: ℞ OF ACUTE LEUKEMIA

Case Report: Edgar W. Age 42. Subacute Lymphocytic Leukemia



Complete Remission for several months



During Remission

Note:

Disabling bone pain completely relieved

Drug reactions: Right lower quadrant abdominal pain. Marked Alopecia.

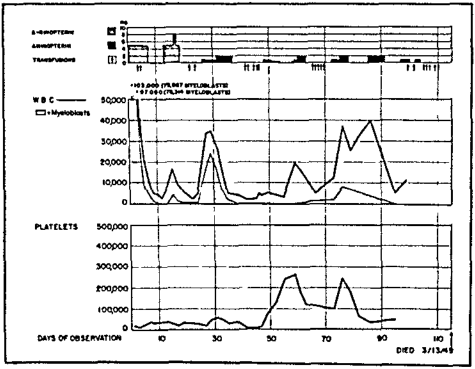
Macrocytosis of Red Cells.

Death in 9½ months

Death due to: Increasing Leukemia
: Increasing Toxicity

FOLIC ACID ANTAGONISTS
℞ OF "MYELOBLAST CRISIS"

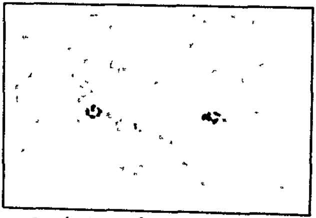
<u>Case Report</u>: Julia S. Chronic Myelocytic Leukemia: ℞ for 5 years with X-rays and Urethane. Sudden onset of acute symptoms. Reversion of Blood Picture from "Chronic" to "Acute" type.



- Remission induced with Folic Acid Antagonist ℞
- Patient lived 4 months (Usual life span in crisis: 1-2 weeks)



Chronic Myelocytic Leukemia
Acute 'Blast Crisis (Nov. 22, 1948)



Remission after Aminopterin
(January 13, 1949)

ACUTE AND SUBACUTE LEUKEMIA

Occur at any age: Most common form of Cancer in Children
Generalized, rapidly progressive, highly invasive processes
Like Weeds in a garden, destroy Normal Marrow Cells
Rapidly Progressive Anemia, Granulocytopenia and Thrombocytopenia

Symptoms those of Anemia, Infection, Bleeding and Invasion of Bone

Course 2 wks. to 6 mos; Spontaneous Remissions rare

TREATMENT

X-rays, Radio-active Phosphorous, Arsenic, Benzol of no value, in fact often harmful.
Transfusions add Red Cells and a few Platelets, help temporarily.
Exsanguino-Transfusions (BESSIS, [PARIS]) may induce Remissions.
Folic Acid Antagonists the first substances producing Remissions consistently

- Acute Leukemia offers a readily available source of Primitive Neoplastic Cells for various experimental and Therapeutic Studies.

FOLIC ACID ANTAGONIST THERAPY OF ACUTE LEUKEMIA

SUMMARY AND CONCLUSIONS

1.) 40 cases treated, 34 adults, 6 children

2) 8 cases died within 1 wk., excluded from evaluation

3.) Remissions in ten (31%) of 32 evaluated cases:

- a. Subjective improvement
- b. Objective improvement
- c. Rise in Platelets to Normal or Near Normal
- d Fall in White Count to Normal or Near Normal
- e Disappearance of 'blasts from blood

Maintenance for at least 2 months

4.) Results: Best in Lymphoblastic type, worst in Monocytic

	CASES	REMISSIONS
Lymphoblastic	14	6
Myeloblastic	11	3
Monocytic	4	0
Unclassified	3	1

Remissions occur in adults as well as in children

5.) 4, Amino - PGA (Aminopterin) the "Standard" drug

A-ninopterin less toxic, almost as effective

6) These drugs do not cure

That they even produce Remissions is remarkable

URETHANE

A Urea product: Ethyl Ester of Carbamic Acid

$$NH_2\text{-}CO\text{-}OC_2H_5$$

Originally used in Anesthesia and Surgery

Mild Anti-Carcinogenic effect noted

Diminished Mitotic Activity of Leukocytes

Development of Leukopenia

Use in Leukemia suggested

Striking effects noted in Chronic Myelocytic Leukemia

Given orally: 1-3 gms. daily

Coated tablets, in syrup

Rectal and Intravenous routes used at times

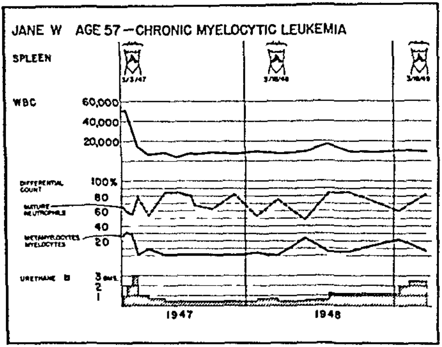
Chief Toxic effects: Anorexia and Indigestion

Chief Uses: In Chronic Myelocytic Leukemia

In Multiple Myeloma

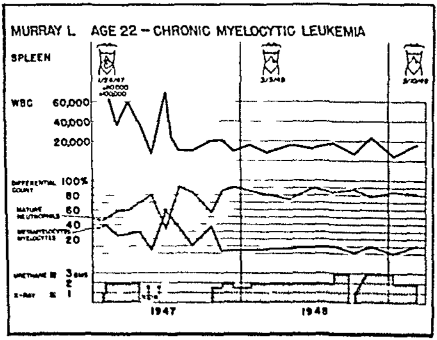
URETHANE
℞ OF CHRONIC MYELOCYTIC LEUKEMIA

Case Reports:



Early Mild Case

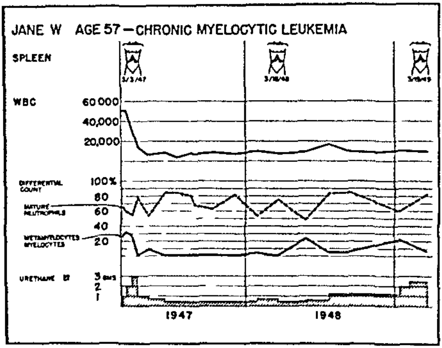
Urethane the sole ℞ used
Almost complete Remission
Splenomegaly persists



Urethane: Slight response
X-ray ℞: Partial Remission
Urethane then produced almost total Remission, now 20 months

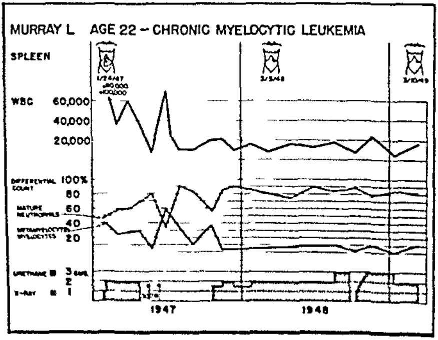
URETHANE
℞ OF CHRONIC MYELOCYTIC LEUKEMIA

Case Reports:



Early Mild Case

Urethane the sole ℞ used
Almost complete Remission
Splenomegaly persists



Urethane: Slight response
X-ray ℞: Partial Remission
Urethane then produced almost total Remission, now 20 months

URETHANE
℞ IN CHRONIC MYELOCYTIC LEUKEMIA
20 Consecutive Cases treated 6-24 months

Dosage: 1-3 gms. daily, given regularly
: "Enscal" coated tablets (0.3 gm. each) T.I.D. P.C.
: Usually given at end of X-ray induced Remission when W.B.C. beginning to rise

Reactions: Gastro-Intestinal: 12 cases
Anorexia, Nausea, Vomiting, Epigastric distress, "Gas"
General: Weakness, 5 cases
Neurological: 3 cases
(1) Symptoms of increased Intracranial Pressure, Papilledema
(2) Blurring of vision, Secondary Optic Atrophy
(3) Paralyses, involvement of Pons
Blood: Thrombocytopenia: 4 cases
Purpura - 1 case
Bleeding from Peptic Ulcer - 1 case

Results:
Remissions well maintained for 3-18 months, if drug tolerated
General health good: Patients ambulatory
Splenomegaly: Slight to moderate reduction
Blood: W.B.C. 5000 - 20,000
Myelocytes greatly reduced
Basophiles elevated
R.B.C. unchanged

Comments: Drug acts as a "brake" to Granulocytic Hyperplasia
Valuable in maintaining & prolonging X-ray induced Remission
Dosage adjusted easily

URETHANE

℞ OF MULTIPLE MYELOMA

Case Report: Edith P. Severe bone pains. Numerous Spontaneous Fractures

Urethane ℞. 2-3 gms daily P.O. begun Nov. 27, 1948

BLOOD - ROULEAUX MARROW - PLASMA CELLS +++



(Nov. 25, 1948)

BLOOD NO ROULEAUX MARROW - ALMOST NORMAL



(Apr. 7, 1949)

Nov. 25, 1948

- Sedimentation Rate 135 mms/hr
- Total protein 9.5 gms
  - Alb. 4.3
  - Glob. 5.2
- Blood Counts: HGB. 10.5 gms
  - R.B.C. 4.15 M
  - W.B.C. 5200

Apr. 7, 1949

- Sedimentation Rate 55 mms/hr
- Total protein 7.5 gms
  - Alb. 4.0
  - Glob. 3.5
- Blood Counts: HGB. 11.0 gms.
  - R.B.C. 3.50 M
  - W.B.C. 3900



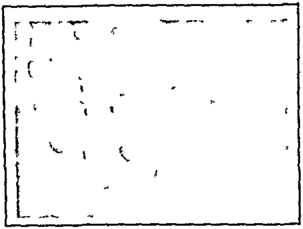
X-ray Clavicle (Jan 5, 1949)



X-ray Clavicle (Apr. 7, 1949)

URETHANE THERAPY OF MULTIPLE MYELOMA

BEFORE Rx

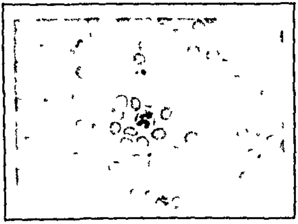


Blood -
Rouleaux Formation

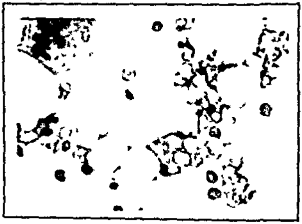


Marrow
Extensive Replacement by Plasmocytic Myeloma Cells

AFTER Rx



Blood -
No Rouleaux Formation

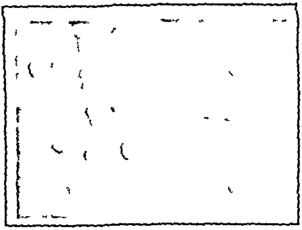


Marrow -
Relative Hypocellularity, great reduction in Plasmocytes

Urethane reduces Plasmocytic Proliferation in Marrow, may slow progression of disease.

URETHANE THERAPY OF MULTIPLE MYELOMA

BEFORE ℞



Blood -
Rouleaux Formation



Marrow
Extensive Replacement by Plasmocytic Myeloma Cells

AFTER ℞



Blood -
No Rouleaux Formation



Marrow -
Relative Hypocellularity, great reduction in Plasmocytes

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URETHANE THERAPY

CONCLUSIONS

1.) No value in Acute Leukemia and Leukosarcoma
2.) Far inferior to X-ray Rx in Chronic Lymphocytic Leukemia
3.) Great value in Chronic Myelocytic Leukemia
    In mild cases may be used as sole Rx
    In severe cases, often prolongs X-ray induced remission 3-18 months
  Remission may be complete
    W.B.C. levels at 5000 - 10,000
    Early Granulocytes diminish or disappear
4.) Easy to Administer
    Control by Internist. No special apparatus
    Discontinuance of drug stops reactions
5) Definite value in Multiple Myeloma
    Relief of Bone Pain; Bone Healing
    Change in Marrow Picture
    Reduction in Abnormal Plasma Proteins
6) Disadvantages:
    Some patients develop marked Anorexia & Indigestion
      Drug discontinued, W.B.C. rises quickly
    Splenomegaly only slightly affected
    Not a cure

URETHANE THERAPY

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    Not a cure

THE ℞ OF LEUKEMIA AND LEUKOSARCOMA

BEST AVAILABLE THERAPY (1949)

LEUKEMIA

• Acute	Myelocytic	Folic Acid Antagonists
	Lymphocytic	Folic Acid Antagonists
	Monocytic	A Nitrogen Mustard (SK 136)
	plus Transfusions; Antibiotics	
• Chronic	Myelocytic	X-rays; RaP; Urethane
	Lymphocytic	X-rays
	Monocytic	HN_2; X-ray
	Plasmacytic (Multiple Myeloma)	Urethane; Stilbamidine RaP may be tried

LEUKOSARCOMA

Lymphosarcoma	Extirpation, if possible X-rays; HN_2, especially if generalized Aminopterin, in special cases, with high degree of cell primitivity
Reticulum Cell Sarcoma	X-rays; HN_2
Hodgkin's Disease	Extirpation, if possible X-rays and HN_2, early cases HN_2, especially if generalized
Plasmacytoma (Local Myeloma)	X-rays; Urethane

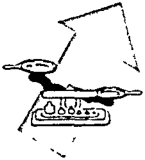
These "Irreversible" Proliferations demand use of all known methods. Each case must be Individualized.

X-RAY THERAPY VS. CHEMOTHERAPY

X-RAY THERAPY

ADVANTAGES

Tried and True
Induces Full Remissions
in early cases of
Chronic Leukemia
Hodgkin's Disease
Lymphosarcoma



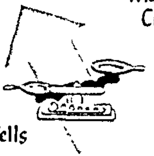
DISADVANTAGES

Non-specific
Affects all cells alike
Requires Special Expensive
Apparatus
Requires Additional Specialist
(Radiologist)
Leads to Divided Responsibility
(Internist Loses Control)
No Value in Acute Leukemia
Little Value in Generalized
Hodgkin's & Lymphosarcomatosis

CHEMOTHERAPY

ADVANTAGES

Affects all parts of body at once
(HN2 intravenously)
Requires no special apparatus
May attack Cells not affected by X-rays
Particularly Valuable in
Generalized Disease
Hodgkin's
Lymphosarcoma
Acute Leukemia
Has many possibilities i.e.
Specific Chemicals for Specific Cells



DISADVANTAGES

Little value in:
Chronic Lymphocytic Leukemia
Solitary Masses of Leukemic
or Sarcomatous Nodes
Marked Splenomegaly of
Chronic Myelocytic Leukemia

CONCLUSIONS X-rays and Chemotherapy each have a job to do.
Both are disappointing since neither cures.
Chemotherapy holds most promise for the future

CHEMOTHERAPY OF LEUKEMIA AND LEUKOSARCOMA

GENERAL SUMMARY

Chemotherapy prolongs life:
- In Hodgkin's disease (HN_2)
- In Lymphosarcoma (HN_2)
- In Acute Leukemia (Aminopterin)

This is a start in the Rx of these "Irreversible" Proliferations

Certain degree of specificity is observed
- HN_2: Hodgkin's disease, Lymphosarcoma
- Urethane: Chronic Myelocytic Leukemia, Myeloma
- Aminopterin: Acute Lymphocytic Leukemia

Studies of cell reactions in Leukemia-Leukosarcoma contribute to Cancer studies in general

Chemotherapy: More a future hope than a present-day cure

Ultimate control of Leukemia-Leukosarcoma will come through integrated efforts of the pure Chemist, the Enzymologist, the Morphologist and the Clinician.

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